Calcium Channel Blockers

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Vasospastic Angina	Angina	Ventricular Rate Control	Hypertension
Dihydropyridines					
amlodipine* (Norvasc®)[1]	generic	X	X	--	X
felodipine ER (Plendil®)[2]	generic	--	--	--	X
isradipine[3]	generic	--	--	--	X
isradipine SR (Dynacirc CR®)[4]	GSK	--	--	--	X
nicardipine (Cardene®)[5]	generic	--	X	--	X
nicardipine SR (Cardene SR®)[6]	Roche	--	--	--	X
nifedipine (Procardia®)[7]	generic	X	X	--	--
nifedipine ER, nifedipine SA, nifedipine SR (Adalat CC®**, Afeditab™ CR, Nifediac CC®, Nifedical XL®, Procardia XL®)[8]	generic	X	X	--	X
nimodipine[9]***	generic				
nisoldipine ER (Sular®)[10]	generic, Sciele Pharma	--	--	--	X
Nondihydropyridines					
diltiazem (Cardizem®)[11]	generic	X	X	X	--
diltiazem ER (Cardizem LA®)[12]	generic	--	X	--	X
diltiazem ER (Cardizem CD®, Cartia XT, Dilacor XR®, Dilt CD, Taztia XT, Tiazac®)[13]	generic	X	X	--	X
diltiazem ER (Dilt XR)[14]	generic	--	X	--	X
diltiazem ER (Diltia XT)[15]	generic	--	X	--	X
verapamil# (Calan®)[16]	generic	X	X	X	X
verapamil ER (Covera-HS®)[17]	Pfizer	--	X	--	X

FDA-Approved Indications (continued)

Drug	Manufacturer	Vasospastic Angina	Angina	Ventricular Rate Control	Hypertension
Nondihydropyridines					
verapamil ER (Verelan PM®)[18]	generic	--	--	--	X
verapamil SR (Calan SR®, Isoptin SR®, Verelan®)[19]	generic	--	--	--	X

*Amlodipine is also indicated for angiographically documented coronary artery disease (CAD) in patients without heart failure or an ejection fraction <40 percent.[20]

**Adalat CC is only indicated for the treatment of hypertension, alone or in combination with other antihypertensive agents.

***Nimodipine is indicated only for use in subarachnoid hemorrhage.

#Verapamil is also indicated for unstable angina.

OVERVIEW

Hypertension affects approximately one-third of adult Americans and only half of this population have their hypertension under control.[21] From 1997 to 2007, the death rate from heart disease declined 27.8 percent, but inpatient cardiovascular operations and procedures increased during the same period by 27 percent.[22] Hypertension is an independent risk factor for the development of cardiovascular disease.[23]The more elevated the blood pressure, the higher the risk of myocardial infarction (MI), stroke, heart failure, and kidney disease. To reduce the risk of cardiovascular events, the current blood pressure goal is less than 140/90 mm Hg. For patients with chronic renal disease or diabetes, the current goal for blood pressure therapy is less than 130/80 mm Hg.[24,25,26] Attainment of blood pressure goals results in a reduced risk of cardiovascular events.[27] There is inter-patient variability in response to various antihypertensive classes. In the absence of compelling indications, reaching target blood pressure is central in determining cardiovascular benefit in patients with hypertension, not the specific agent used.[28,29,30,31]

Calcium channel blockers (CCBs) are widely used in the treatment of hypertension and angina pectoris. First-line therapy for HTN according to The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7), published in 2003, is diuretics. According to JNC-7, CCBs may be used in patients who have diabetes or are at high risk for coronary heart disease.[32] The American Diabetes Association (ADA) 2009 guidelines recommend that dihydropyridine (DHP) CCBs be used as second-line drugs for patients with diabetes and hypertension who cannot tolerate the other preferred classes [angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), or thiazide diuretics] or require additional agents to achieve the target blood pressure.[33] Since the publication of JNC-7 and ADA guidelines for the treatment of hypertension, a meta-analysis aimed at evaluating the blood pressure lowering effects and incidences of heart attach, stroke and death in patients taking HCTZ has been published.[34] Based on 14 studies including 1,234 patients taking HCTZ, blood pressure lowering with HCTZ was inferior to all other classes, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and calcium antagonists. Additionally, the meta-analysis concluded that there are no studies or evidence that HCTZ reduces myocardial infarction, stroke, or death.

Several trials have shown that long-acting CCBs have decreased hospitalization and revascularization procedures associated with them.[35,36,37,38]

Hypertension

CCBs have been shown to effectively reduce blood pressure. In isolated systolic hypertension (ISH), CCBs have been shown to reduce the systolic blood pressure (SBP) more than diastolic blood pressure (DBP), thereby reducing the pulse pressure. In patients with ISH, treatment with nitrendipine, a CCB not available in the U.S., reduced the stroke rate by 42 percent and cardiovascular morbidity by 30 percent.[39] In the ALLHAT study, the primary endpoint of combined fatal CHD and nonfatal acute MI were similar amongst chlorthalidone, amlodipine, and lisinopril treatment arms. Amlodipine demonstrated higher risk of heart failure and hospitalization related to heart failure or fatal heart failure compared to chlorthalidone, among diabetics and non-diabetics [RR 1.42, 95% confidence interval (CI), 1.23 to 1.64]. CCBs and diuretics in other comparative published trials have been shown to have similar risk reductions and rates of major CHD events and stroke.[40,41,42,43,44] An ALLHAT post-hoc analysis found that in patients with metabolic syndrome, particularly in African-American patients, the findings do not support preferring a CCB, ACE inhibitor, or alpha blocker to a thiazide diuretic despite their more favorable metabolic profiles.[45] A subgroup analysis of ALLHAT showed that despite a less favorable metabolic profile, thiazide-like diuretic initial therapy for hypertension offers similar, and in some instances possibly superior, cardiovascular disease outcomes in older hypertensive adults with metabolic syndrome, as compared with treatment with CCBs and ACE inhibitors.[46] A post-hoc analysis of the ALLHAT data demonstrated a higher risk of heart failure with amlodipine and lisinopril versus chlorthalidone in the first year. The unadjusted risk of hospitalized or fatal heart failure remained higher for amlodipine versus chlorthalidone (RR 1.35, 95% CI, 1.21 to 1.5) and lisinopril (RR 1.23, 95% CI, 1.09 to 1.38).[47]

Several large clinical trials have compared CCBs with other types of antihypertensives. Some of the recent trials in patients with hypertension include ALLHAT, VALUE, INVEST, CONVINCE, and ASCOT-BPLA.[48,49,50,51,52] The comparator antihypertensives have included ACE inhibitors, diuretics, angiotensin receptor blockers, beta-blockers, and combinations of antihypertensives. Many of these large trials have demonstrated that CCBs have beneficial effects on composite cardiovascular outcomes or individual clinical outcomes. However, most of the trials only demonstrate equivalence to the comparator antihypertensives rather than superiority.[53,54,55]

Angina

CCBs improve clinical symptoms and are well tolerated. Long-acting CCBs are recommended for the treatment of chronic stable angina when beta-blockers are not tolerated or do not relieve symptoms.[56,57] Vasospastic (or Prinzmetal's) angina is effectively treated with CCBs by reducing the frequency of anginal attacks.

PHARMACOLOGY[58,59]

CCBs inhibit calcium ions from moving across the cell membrane. The limitation of calcium entering into the cells causes a decrease in mechanical contraction of myocardial and smooth muscle, thereby causing dilation of systemic arteries and a decrease in total peripheral resistance, systemic blood pressure, and the afterload of the heart. The reduction in afterload, which results in a decrease in myocardial oxygen consumption, is thought to be responsible for the CCB benefit in angina. There are

three classes of CCBs: diphenylalkylamines (e.g., verapamil), benzothiazepines (e.g., diltiazem), and dihydropyridines (e.g., amlodipine, felodipine ER, isradipine, nicardipine, nifedipine, and nisoldipine ER). The dihydropyridines are potent vasodilators and can increase or have a neutral effect on vascular permeability.[60] The nondihydropyridine verapamil, and to a lesser extent, diltiazem, are less potent vasodilators, but they have a greater depressive effect on cardiac conduction and contractility.

PHARMACOKINETICS

Drug	Bioavailability (%)	Half-Life (hr)	Metabolism	Excretion (%)
Dihydropyridines				
amlodipine (Norvasc)[61]	64-90	30-50	Inactive metabolites	Urine: 60
felodipine ER (Plendil)[62]	20	11-16 for immediate release	Six inactive metabolites; concentration is 23 percent of parent	Urine: 70 Feces: 10
isradipine/SR (Dynacirc CR)[63]	15-24 (Dynacirc CR)	8	Several inactive metabolites	Urine: 60-65 Feces: 25-30
nicardipine/SR (Cardene/SR)[64,65]	35	11.5	Metabolized extensively	Urine: 60 Feces: 35
nifedipine (Procardia/XL)[66, 67]	40-77 (Procardia) 86 (Procardia XL relative to IR)	2	Inactive metabolites	Urine: 60-80
nimodipine[68]	13	1-2	Inactive metabolites	--
nisoldipine ER (Sular)[69]	5	7-12	5 metabolites; one active, 10 percent activity of parent; concentration equal to parent	Urine: 60-80
nisoldipine ER new formulation (Sular)[70]	5	13.7	5 metabolites; one active, 10 percent activity of parent; concentration equal to parent	Urine: 60-80
Nondihydropyridines				
diltiazem (Cardizem)[71]	40-60	3.5-9	desacetyl diltiazem is 25-50 percent as potent as parent; concentration is 10-20 percent of parent	--
diltiazem ER (Cardizem LA)[72]	40	6-9	desacetyl diltiazem is 25-50 percent as potent as parent; concentration is 10-20 percent of parent	--
diltiazem ER (Cardizem CD)[73]	--	5-8	--	--
verapamil (Covera HS, Verelan PM)[74,75]	33-65 (varies with rate and extent of release from dosage forms)	4.5-20	13 metabolites; norverapamil is 20 percent as potent as parent; concentration equal to parent	Urine: 70-74 Feces: 16

Chronotherapeutics is the concept of administering antihypertensives by delayed release mechanisms to lower blood pressure during the rapid rise associated with awakening. It is unclear if this concept actually lowers morbidity and mortality.[76]

CONTRAINDICATIONS/WARNINGS

Nicardipine is contraindicated in patients with advanced aortic stenosis. Reduction of DBP in these patients may worsen rather than improve myocardial oxygen balance.[77] Peripheral edema is a common adverse event of CCBs and usually occurs within two to three weeks of starting therapy.

Short-acting nifedipine has been related to increased coronary mortality rates in patients with a history of MI and should not be used for the treatment of hypertension.[78,79]

Diltiazem and verapamil are contraindicated in sick sinus syndrome (except in patients with a functioning artificial pacemaker), second or third degree atrioventricular block (except in patients with a functioning artificial pacemaker), hypotension (SBP<90 mm Hg), or cardiogenic shock. Diltiazem is contraindicated in acute myocardial infarction (MI) and pulmonary congestion. Verapamil is contraindicated in severe left ventricular dysfunction, atrial flutter or fibrillation with an accessory bypass tract (Wolff-Parkinson-White syndrome or Lown-Ganong-Levine syndrome). Diltiazem and verapamil should be used with caution in hepatic or renal dysfunction.[80,81,82,83,84]

Nimodipine capsules should not be administered intravenously or by any other parenteral method as this could result in death.[85] Short-acting nifedipine has been related to increased coronary mortality in patients with a history of MI and should not be used for the treatment of hypertension.[86,87]

There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of Procardia XL (GITS tablet formulation). Bezoars can occur in very rare cases and may require surgical intervention.[88] Risk factors for a gastrointestinal obstruction identified from post-marketing reports of Procardia XL include alteration in gastrointestinal anatomy (e.g., severe gastrointestinal narrowing, colon cancer, small bowel obstruction, bowel resection, gastric bypass, vertical banded gastroplasty, colostomy, diverticulitis, diverticulosis, and inflammatory bowel disease), hypomotility disorders (e.g., constipation, gastroesophageal reflux disease, ileus, obesity, hypothyroidism, and diabetes) and concomitant medications (e.g., H2-histamine blockers, opiates, nonsteroidal anti-inflammatory drugs, laxatives, anticholinergic agents, levothyroxine, and neuromuscular blocking agents). Cases of tablet adherence to the gastrointestinal wall with ulceration have been reported, some requiring hospitalization and intervention.

DRUG INTERACTIONS

Nifedipine and nisoldipine should not be administered with grapefruit juice.[89,90,91] Nifedipine ER and Felodipine ER may increase tacrolimus serum levels.[92,93]

Blood pressure lowering effects may be additive when used concurrently with sildenafil (Viagra®, Revatio™), tadalafil (Cialis®, Adcirca™), and vardenafil (Levitra®).

Diltiazem and verapamil both inhibit CYP3A4; both can increase the effects of amiodarone, beta-blockers, lithium, digoxin, carbamazepine, and selected HMG-CoA reductase inhibitors (statins). For statins given with diltiazem, limit the dose of simvastatin to 10 mg daily and diltiazem to 240 mg daily. For statins coadministered with verapamil, limit the dose of simvastatin to 10 mg daily and lovastatin to 40 mg daily.

Amlodipine is a CYP3A4 substrate. Coadministration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77 percent increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.[94]

Grapefruit juice can increase verapamil serum concentrations, and to a lesser extent, diltiazem serum concentrations.[95,96,97,98,99]

Cardiovascular action of other CCBs may be enhanced by the addition of nimodipine.[100]

ADVERSE EFFECTS

Drug	AV Block	Constipation	Dizziness	Edema	Fatigue	Flushing	HA	Nausea
Dihydropyridines								
amlodipine (Norvasc)[101] n=1,730 (placebo n=1,250)	nr	< 1	1.1-3.4 (1.5)	1.8–10.8 (0.6)	4.5 (2.8)	0.7 – 2.6 (0)	7.3 (7.8)	2.9 (1.9)
felodipine ER (Plendil)[102] n=861 (placebo n=334)	nr	0.3 – 1.5 (0.9)	2.7 – 3.7 (2.7)	2 – 17.4 (3.3)	nr	3.9 – 6.9 (0.9)	10.6 – 14.7 (10.2)	1 – 1.7 (1.5)
isradipine IR[103]	nr	nr	7.3 (4.4)	7.2 (3)	3.9 (0.3)	2.6 (0)	13.7 (14.1)	1.8 (1.7)
isradipine SR (Dynacirc CR)[104] n=422 (placebo n=186)	nr	1.7 (0)	4.7 (2.7)	15.2 (2.2)	4.3 (2.2)	1.9 (0.5)	13 (12.4)	1.2 (1.6)
nicardipine (Cardene)[105,106] n=1,390 (placebo n=211)	nr	0.2-0.6 (0-0.6)	1.8-4 (0)	0.3-8 (0-1.4)	nr	2.1-9.7 (0-2.8)	2.6-8.2 (0-4.7)	0.9-2.2 (0-0.9)
nicardipine SR (Cardene SR)[107,108] n=322 (placebo n=140)	nr	nr	1.6 (0.7)	5.9 (1.4)	nr	nr	6.2 (7.1)	1.9 (0.7)
nifedipine (Procardia)[109] n=226 (placebo n=235)	nr	<2	27 (15)	7 (1)	nr	25 (8)	23 (20)	11 (8)
nifedipine SR (Procardia XL)[110] n=707 (placebo n=266)	nr	3.3 (2.3)	4.1 (4.5)	10 – 30	5.9 (4.1)	< 3	15.8 (9.8)	3.3 (1.9)
nimodipine[111,112] n=823 (placebo n=479)	nr	nr	<1	0.4-1.2 (0.6)	nr	nr	1.2-1.4 (0.2)	0.6-1.2 (0)
nisoldipine ER (Sular)[113] n=663 (placebo n=280)	≤ 1	nr	3-7 (4)	7-27 (10)	nr	nr	22 (15)	2 (1)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all-inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

Adverse Effects (continued)

Drug	AV Block	Constipation	Dizziness	Edema	Fatigue	Flushing	HA	Nausea
Nondihydropyridines								
diltiazem ER (Cardizem LA)[114]	3.2	< 1	6.4	6.8	4.8	1.4	4.6	1.4
diltiazem ER (Cardizem CD) [115] n=607	3.3 (0)	< 1	3 (3)	2.6 (1.3)	nr	1.4	5.4 (5)	1.4
verapamil ER (Covera-HS)[116] n=572 (placebo n=261)	1.7 (0)	11.7 (2.7)	4.7 (2.7)	3 (3.1)	4.5 (3.8)	0.8 (0.3)	6.6 (7.3)	2.1 (1.9)
verapamil ER (Verelan PM)[117,118] n=297 (placebo n=116)	nr	8.8 (0.9)	3 (0.9)	1.7 (0)	nr	nr	12.1 (11.2)	1.7 (0)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all-inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

SPECIAL POPULATIONS

Pediatrics

Amlodipine has been studied in a randomized, double-blind, placebo-controlled, parallel-group study with 268 hypertensive children (mean age, 12.1 ± 3.3 years).[119] Amlodipine reduced blood pressure in a dose-dependent manner with good tolerability, and only two percent of children discontinued therapy related to adverse effects. The effective antihypertensive oral dose of amlodipine in pediatric patients aged six to 17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients[120].

Safety and efficacy of other CCBs in hypertensive pediatrics have not been established.[121] Many of the CCBs are extended release products, making them difficult to use in children.

Pregnancy

All products in this class are Pregnancy Category C.[122]

Hepatic/Renal Impairment

Amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine ER, diltiazem, and verapamil may require dose adjustment in hepatic impairment or in cirrhosis. Nicardipine, diltiazem, and verapamil may require dose adjustment in renal impairment.[123]

DOSAGES

Drug	Initial HTN Dose	Maximum HTN Dose	Angina Dose	Availability
Dihydropyridines				
amlodipine (Norvasc)[124]	5 mg daily	10 mg daily	5-10 mg daily	2.5, 5, 10 mg tablets
felodipine ER (Plendil)[125]	5 mg daily	10 mg daily	--	2.5, 5, 10 mg tablets
isradipine[126]	2.5 mg twice daily	10 mg twice daily	--	2.5, 5 mg capsules
isradipine SR (Dynacirc CR)[127]	5 mg daily	20 mg daily	--	5, 10 mg tablets
nicardipine (Cardene)[128]	20 mg three times a day	40 mg three times a day	20-40 mg three times a day	20, 30 mg capsules
nicardipine SR (Cardene SR)[129]	30 mg twice daily	60 mg twice daily	--	30, 45, 60 mg capsules
nifedipine[130]	--	--	10 mg three times a day to max of 30 mg per dose or 180 mg per day	10, 20 mg capsules
nifedipine SR[131]	Adalat CC, Procardia XL: 30-60 mg daily	Adalat CC: 90 mg Procardia XL: 120 mg daily	Adalat CC, Procardia XL: 30-90 mg daily	ER tablet: 30, 60, 90 mg tablets Adalat CC, Procardia XL, Nifediac CC: 30, 60, 90 mg tablets Afeditab CR, Nifedical XL: 30, 60 mg tablets
nimodipine[132]	--	--	--	30 mg capsules
nisoldipine ER[133]	20 mg daily	60 mg daily		ER tablet: 20, 30, 40 mg tablets
nisoldipine ER (Sular)[134]	17 mg daily	34 mg daily	--	8.5, 17, 25.5, 34 mg tablets (new formulation)

Nimodipine is administered as 60 mg every four hours for 21 days for the reduction of the incidence and severity of ischemic deficits associated with subarachnoid hemorrhage.[135]

Nisoldipine ER generic tablets and Sular tablets are not AB-rated and are not interchangeable.

Dosages (continued)

Drug	Initial HTN Dose	Maximum HTN Dose	Angina Dose	Availability
Nondihydropyridines				
diltiazem (Cardizem)[136]	--	--	30 mg four times daily to a max of 360 mg per day	30, 60, 90, 120 mg tablets
diltiazem ER[137,138]	120-240 mg daily	480 mg daily Tiazac: 540 mg daily	120-480 mg daily Tiazac: 120-540 mg daily	ER capsules: 120, 180, 240, 300, 360, 420 mg capsules Cardizem CD, Cartia XT, Dilacor XR, Diltia XT, Dilt CD, Dilt XR, Taztia XT, Tiazac: 120, 180, 240 mg capsules Cardizem CD, Cartia XT, Dilt CD, Taztia XT, Tiazac: 300 mg capsules Cardizem CD, Taztia XT, Tiazac: 360 mg capsules Tiazac: 420 mg capsules
diltiazem ER (Cardizem LA)[139]	180-240 mg daily	540 mg daily	180-360 mg daily	120, 180, 240, 300, 360, 420 mg tablets
verapamil (Calan)[140]	80 mg three times daily	480 mg per day	80 mg-120 mg three times daily up to a max of 480 mg per day	40, 80, 120 mg tablets
verapamil ER (Covera HS)[141]	180 mg at bedtime	480 mg at bedtime	180-480 mg at bedtime	180, 240 mg tablets
verapamil ER (Verelan PM)[142]	200 mg at bedtime	400 mg at bedtime	--	100, 200, 300 mg capsules
verapamil SR[143]	240 mg daily	480 mg daily	--	Calan SR, Isoptin SR: 120, 180, 240 mg tablets
verapamil SR (Verelan)[144]	240 mg daily	480 mg daily	--	120, 180, 240, 360 mg capsules

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class and the FDA-approved indications. Comparative clinical trials have been performed with some of the agents in this class. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not

suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Many clinical studies were performed in the 1980 and 1990s evaluating the hemodynamic effects of the CCBs; however, clinical trials with clinical endpoints have more recently been published.

amlodipine (Norvasc) and nicardipine (Cardene)

Amlodipine and nicardipine were compared in a randomized, double-blind trial evaluating efficacy in 133 patients with ISH.[145] Patients were over 60 years old. Patients were randomized to amlodipine 5 mg once daily or nicardipine 60 mg per day (given in two or three divided doses). Doses were titrated up if necessary for BP control with maximum doses of amlodipine 10 mg daily and nicardipine 100 mg per day given in divided doses. After 90 days, the office blood pressure and ambulatory blood pressure monitoring (ABPM) were significantly reduced in terms of SBP and pulse pressure by both therapies. Per ABPM studies, amlodipine had a greater effect on the SBP than nicardipine. Therapy was well tolerated.

amlodipine (Norvasc) and nisoldipine ER (Sular)

In a randomized, double blind, double-dummy, parallel group trial, amlodipine and nisoldipine ER were compared for efficacy, safety, and tolerability in 120 patients with stage one to two hypertension (DBP of 90 to 109 mm Hg) and chronic stable angina.[146] The initial phase was a three-week placebo run-in phase followed by the randomization to nisoldipine ER 20 or 40 mg once daily or amlodipine 5 or 10 mg once daily. Doses were titrated if needed after two weeks to achieve a DBP of less than 90 mm Hg. At six weeks, nisoldipine ER (-15/-13 mm Hg) and amlodipine (-13/-11 mm Hg) effectively reduced blood pressure (p=NS). Blood pressure response rates for nisoldipine ER (87 percent) and amlodipine (78 percent) were similar (p=NS). The mean increase in total exercise time was similar in both groups (p=NS). More headache and peripheral edema were observed with nisoldipine ER, but overall, both therapies were well tolerated.

Nisoldipine ER and amlodipine were compared in 192 African-American patients with DBP of 95 to 114 mm Hg over 12 weeks.[147] Patients were randomized to nisoldipine ER 20 to 60 mg daily or amlodipine 5 to 10 mg daily in a double-blind manner. Blood pressure, using ambulatory monitoring, was significantly lower compared to baseline with nisoldipine ER (-23/-16 mm Hg) and amlodipine (-20/-15 mm Hg) (between-group comparisons, p=0.07 for SBP; p=0.5 for DBP). Neither agent had an effect on heart rate. Adverse effects were similar for both groups; most commonly reported were headache, edema, and dizziness.

diltiazem ER (Cardizem LA) and amlodipine (Norvasc)

Diltiazem ER and amlodipine were compared in 262 hypertensive African-Americans in a multicenter, randomized, double-blind, parallel-group, dose-to-effect study.[148] Patients were randomized to diltiazem ER 360 mg at bedtime (10 p.m.) or morning amlodipine 5 mg (8 a.m.) for six weeks; if blood pressure still exceeded 130/85 mm Hg, therapy was titrated to diltiazem ER 540 mg or amlodipine 10 mg. Changes in blood pressure, heart rate, and rate-pressure product (heart rate x SBP) were measured by ambulatory blood pressure monitoring for the first four hours after awakening and over a 24-hour period. Amlodipine increased heart rate whereas diltiazem ER decreased heart rate. Greater mean reductions in heart rate and rate-pressure product were seen in the diltiazem group during all

intervals (p≤0.0008). Diltiazem ER showed greater reductions in DBP during the first four hours after awakening and between 6 a.m. and noon (p<0.0049 and p<0.0019), but had a comparable reduction in the mean 24-hour DBP to amlodipine. Reductions in the SBP in the morning hours were comparable for both groups; however, amlodipine demonstrated a 3.4 mm Hg greater reduction in the mean 24-hour SBP (p<0.0022). Both arms were well tolerated. The manufacturer of diltiazem ER funded the study.

felodipine ER (Plendil) and amlodipine (Norvasc)

In a multicenter, double-blind, parallel group trial, felodipine ER and amlodipine were compared in 535 elderly hypertensive patients (> 65 years).[149] Patients had an initial sitting DBP of 90 to 115 mm Hg or SBP of 160 to 220 mm Hg. Patients were randomized to felodipine ER 2.5 mg or amlodipine 5 mg once daily. Blood pressure was evaluated after three and six weeks; if BP reduction was not satisfactory, doses were titrated upward. After nine weeks, the average doses of felodipine ER and amlodipine were 5.5 mg and 7.3 mg. The primary endpoint of new vasodilatory adverse effects was reported by 32 percent of the felodipine ER group and 43 percent of the amlodipine group (p=0.007). Both treatments effectively reduced blood pressure 24 hours post-dose.

felodipine ER (Plendil) and nisoldipine ER (Sular)

A multicenter, randomized, double-blind trial compared the safety and efficacy of nisoldipine ER 20 to 40 mg daily and felodipine ER 5 to 10 mg daily in 229 patients with mild to moderate hypertension.[150] Following a two-week placebo run-in phase, patients were randomized and followed for 16 weeks. Both drugs demonstrated significant reductions in blood pressure compared to baseline. No significant differences in blood pressure reduction were observed between the two drugs. The percentage of responders was 77.8 and 66.5 percent for nisoldipine ER and felodipine ER, respectively, Edema occurred more frequently with nisoldipine ER (30 percent) compared to felodipine ER (21 percent). More patients withdrew from the nisoldipine ER group than felodipine ER group with the most common reason being edema.

nifedipine gastrointestinal therapeutic system (GITS)

The ACTION trial was a randomized, double-blind trial evaluating the effects of nifedipine GITS on long-term outcome in 7,665 patients with stable angina.[151] Patients with stable CAD were randomized to nifedipine GITS 60 mg daily or placebo. The primary endpoint, the composite of death, acute MI, refractory angina, new overt heart failure, debilitating stroke, or peripheral revascularization, was similar in both groups {nifedipine 4.6 per 100 patient-years; 4.75 per 100 patient-years for placebo (0.97 [0.88 to 1.07], p=0.54)}. With nifedipine GITS, rate of death and any cardiovascular event or procedure was 9.32 per 100 patient-years versus 10.50 per 100 patient-years for placebo (0.89 [0.83 to 0.95], p=0.0012). Fewer patients underwent coronary angiography and interventions with nifedipine GITS.

nifedipine CC and amlodipine (Norvasc)

A total of 207 patients were enrolled in a randomized, double-blind parallel-group study to compare the antihypertensive efficacy and safety of nifedipine coat-core 30 mg to amlodipine 5 mg.[152] After four weeks of double-blind therapy, patients with a trough seated DBP ≥ 90 mm Hg received an increased dose of nifedipine coat-core 60 mg or amlodipine 10 mg. In the patients with available data (n=176), mean blood pressure decreased from 160.9/101.9 mm Hg to 141.3/85.5 mm Hg in the

nifedipine group and from 160.5/101.8 mm Hg to 140.7/85.9 mm Hg in the amlodipine group. Both drugs were well tolerated, with equivalent antihypertensive efficacy, and similar safety profiles.

nisoldipine ER (Sular)

The NICOLE study determined the effects of nisoldipine ER on the rate of progression of coronary atherosclerosis and the rate of clinical cardiovascular events.[153] The single-center, double-blind, randomized, placebo-controlled study enrolled 826 patients who had undergone coronary angioplasty. Patients were randomized to nisoldipine ER 40 mg daily or placebo and followed for up to three years. No significance difference was observed between the groups for the number of new coronary lesions. The average minimum luminal diameter of the non-dilated coronary lesions decreased in both groups; however, the difference between the groups was not significant. Both groups demonstrated progression of atherosclerosis in at least one coronary arterial segment, which was defined as an increase in diameter stenosis of ≥ 13 percent. Rates of death, stroke, and MI were similar between the groups; however, revascularizations were less frequent with nisoldipine ER. Therefore, nisoldipine ER patients had overall fewer clinical events compared to placebo (44.6 versus 52.6 percent, p=0.02).

controlled-onset extended release verapamil (Covera-HS) and nifedipine GITS (Procardia XL)

In a prospective, double-blind, randomized trial to compare 24-hour blood pressure control, controlled-onset extended release verapamil and nifedipine GITS were administered to 557 hypertensive patients over ten weeks.[154] Dose titration was based on blood pressure readings at baseline, four weeks, and ten weeks. The four-hour time period of one hour prior to awakening to three hours after awakening was the focus of intense evaluation. Early morning blood pressure was reported to be similar between the two groups. Nifedipine GITS lowered blood pressure significantly more during sleep (-11 mm Hg in the nifedipine GITS group versus -5.8 mm Hg in the verapamil group). Both drugs effectively reduced blood pressure throughout 24 hours.

chronotherapeutic oral drug absorption system (CODAS) verapamil (Verelan PM)

In a randomized, double-blind, placebo-controlled trial, CODAS verapamil was evaluated for efficacy in blood pressure reduction in 277 patients with mild to moderate hypertension.[155] All patients received placebo for two to four weeks prior to randomization. During the run-in placebo phase, patients must have had an initial sitting DBP of 95 to 115 mm Hg. Patients were then randomized in a double-blind manner to CODAS verapamil of 100, 200, 300, or 400 mg or placebo to be taken between 9 p.m. and 11 p.m for eight weeks. Blood pressure was measured weekly and ambulatory blood pressure monitoring was obtained. The 200, 300, and 400 mg doses of CODAS verapamil were effective in lowering DBP compared to placebo. Blood pressure reductions were the greatest between 6 a.m. and noon. Dose-dependent blood pressure reductions were observed. Adverse events were reflective of other verapamil preparations.

META-ANALYSIS

A meta-analysis of 13 major studies with nearly 104,000 pooled hypertensive patients suggests that the dihydropyridine CCBs were associated with a lower risk of stroke compared to other randomized antihypertensives (p=0.006).[156]

SUMMARY

The benefits of CCBs in controlling angina and hypertension are clearly documented. No CCB has demonstrated a clinical advantage over other CCBs in the treatment of hypertension. The dihydropyridine CCBs cause a baroreceptor-mediated reflex increase in heart rate because of their potent peripheral vasodilating effects. Diltiazem decreases atrioventricular conduction and heart rate. Verapamil decreases heart rate, slows atrioventricular nodal conduction to the greatest extent of the CCB and is useful for supraventricular tachyarrhythmias.

The JNC-7 report on the treatment of hypertension recommends diuretics as a part of most antihypertensive regimens. The JNC-7 report lists compelling indications for CCBs for high-risk CHD patients and diabetic patients. CCBs should generally be used in combination with other antihypertensive agents in these two patient groups. Short-acting nifedipine has been related to increased coronary mortality rates in patients with a history of MI and should not be used for the treatment of hypertension.

The effect on cardiovascular morbidity and mortality with CCBs compared to other agents such as diuretics and ACE inhibitors had been less clear until the ALLHAT study, which enrolled patients with hypertension with a known risk factor for CAD, showed that chlorthalidone, amlodipine, and lisinopril had similar outcomes of combined fatal CHD and nonfatal MI. The ALLHAT study confirmed that diuretics should be first-line in the treatment of hypertension. Thiazides, particularly at higher doses, have been shown to induce metabolic abnormalities and should be used with caution.

Several recent trials, such as the CAMELOT study in patients with CAD and normal blood pressure, the NICOLE study in patients with coronary atherosclerosis, and the ACTION study in patients with CAD and stable angina, have demonstrated decreased hospitalization and revascularization procedures associated with several long-acting CCBs.

Many large trials enrolling patients with hypertension, including ALLHAT, VALUE, INVEST, CONVINCE, and ASCOT-BPLA, have demonstrated that CCBs have beneficial effects on composite cardiovascular outcomes or individual clinical outcomes; however, most of the trials only demonstrate equivalence to the comparator antihypertensives rather than superiority.

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